Latency Reversing Agents induce HIV-1 protein expression in latently infected cells for CTL viral recognition and killing

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SHOCK & CTL kill strategies

• To design effective therapeutic strategies to achieve the cure or the functional remission of HIV-1 infection is a major priority in the field.

• **SHOCK**: Latency reversing agents (LRAs)
• **KILL**: Cytotoxic T Lymphocytes (CTL), role in the control of HIV-1 reservoir in spontaneous controllers and EC
AIM: To investigate the impact of LRA treatments in CTL recognition of HIV-1 reactivated cells
LRA inducible HIV-1 in vitro expression: the RELI model

“Resting like” HIV-1 reactivation model (RELI)

HIV-1 (NL43-GFP) → d3 GFP-ve → d7 +PI → LRAs +RLT → SHOCK & CTL KILL

SHOCK

Untreated
PNBN
PNBN/Bryo

Freq-p24 (%)
HIV-1 reactivation following LRAs treatment single or in combination
HIV-1 antigen presentation and CTL recognition in LRAs treated latently infected cells

**SHOCK**
- CD4 HIV-1
- HLA-I B*2705
- WASH

**CTL KILL**
- CD4 HIV-1: CTL HLA-I match
- 20h +RLT
- CTL SENSING CD107a/MIP1β
- CTL KILLING P24

**Graphs**
- % CD107a/MIP1
  - CTL1 and CTL2
  - Treatments: untreated, DMSO, PMA/IO, Tricho, Tricho/Bryo, PNBN, PNBN/Bryo, SAHA, SAHA/Bryo

**Peptide concentration (M)**
- Reactivated and untreated conditions

**Comparison**
- Peptide concentration range from $10^{-3}$ to $10^{-11}$ M
- % CD107a/MIP1 variation with peptide concentration
HIV-1 reactivation by LRAs correlate with CD107a/MIPβ cytokine expression in CTLs

CTL1; Spearman 0.88; P=0.031
CTL2; Spearman 0.99; P=0.0004
LRAs induce HIV-1 specific CTL killing of reactivated cells but do not complete their elimination.

% CTL KILLING OF THE REACTIVATED FRACTION

PROVIRAL HIV-1 DNA
Impact of CTL immune exhaustion in HIV-1 reactivation

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Legend:
- PD1: Red
- CD39: Blue
Presence of “Polyexhausted” CTLs impair the clearance of HIV-1 reactivated cells
Summary

✓ We have developed a new “Tool for Cure” the RELI model, where we can monitor HIV-1 SHOCK & CTL KILL in a single-assay

GOOD NEWS:

✓ There is no interference for CTL recognition of reactivated cells upon LRA treatment

✓ CTLs can recognize and kill LRA HIV-1 reactivated cells decreasing the number of infected cells and the level of the viral reservoir

BAD NEWS:

✓ Differences in TCR avidity impact CTL responsiveness to HIV-1 LRA reactivated cells

✓ There is a small fraction of LRA reactivated cells not killed by CTLs (0.2-0.6%)

✓ “Polyexhausted” CTLs impair the killing of HIV-1 reactivated cells
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